CASE REPORTS

From the New England Society for Vascular Surgery

Contiguous bilateral head and neck paragangliomas in a carrier of the SDHB germline mutation

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Paragangliomas are extremely rare neoplasms with multicentric presentation usually linked to familial tumor syndromes. This patient presented with the uncommon combination of concurrent bilateral carotid body tumors and a unilateral glomus jugulare mass that demonstrated vascular continuity. During treatment, the patient was found to be heterozygous for the SDHB germline mutation, an autosomal dominant genotype of the familial paraganglioma syndromes associated with increased malignancy. The unique profile of the SDHB patient as regards primary evaluation, surgical considerations, and extended surveillance was explored and has led to a proposed treatment algorithm for these patients. (J Vasc Surg 2012;55:216-9.)

A 51-year-old gentleman was referred from an ear, nose, and throat physician following complaints of hearing impairment that was shown on imaging to be secondary to a skull base mass; a large ascending carotid body tumor was concurrently noted. The patient had +2 palpable carotid pulses and no notable cervical masses. Neurologic assessment was without focal motor or sensory deficits, apart from diminished auditory capability.

Computed tomography (CT) scanning in combination with a previously undertaken angiogram demonstrated masses at the right carotid bifurcation ($2.7 \times 2.3 \times 3.7$ cm) and right jugular fossa consistent with paragangliomas (PGLs; Fig 1). The ascending pharyngeal artery acted as a common feeding vessel. Magnetic resonance imaging (MRI) of the head showed an enhancing, lobulated mass ($1.7 \times 1.5 \times 2.4$ cm) that extended through the skull base from the internal auditory canal into the jugular foramen (Fig 2). Further delineation of a smaller left-sided carotid body tumor ($9 \times 8 \times 15$ mm) was undertaken during postoperative CT angiogram imaging.

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Surgical exploration of the right carotid mass revealed a large tumor (Shamblin type 3)[1] that expanded into the posterior common carotid artery and encapsulated the carotid branches. An extensive dissection up to the digastricus ended in removal of the tumor, external carotid sacrifice, and application of a bovine patch to the common and internal carotid arteries where close adherence of the tumor had made for difficult partition. Postoperative examination yielded no focal motor or sensory deficits.

Due to its unilateral presentation and the increased morbidity associated with surgical resection,[2,3] the patient elected for treatment of his glomus jugulare tumor by radioablation. The right jugular fossa received 2400 cGy utilizing CyberKnife radiotherapy; no regrowth was noted at 2-year follow-up.

As regards to the left carotid body tumor, the patient initially refused further surgical intervention, largely due to psychosocial issues. However, 3 years later, the patient elected to return for resection. Removal of this mass was complicated by a posterior pattern of growth and incorporation of the vagus nerve into the dense tumor capsule. Postoperative pathology of both carotid body tumors yielded encapsulated tissue organized into zellballan clusters, a finding pathognomonic to neuroendocrine tumors.

Following his resections, the patient enjoyed uneventful postoperative courses without neurologic or vascular instability. Genetic testing performed at the time of the left carotid surgery returned positive for the sequence change SDHB, I127S (exon 4, c.380T > G, p. I127S). Considering the increased malignancy potential associated with the SDHB mutation, we recommended that the patient's primary medical oversight be transitioned to a specialty cancer

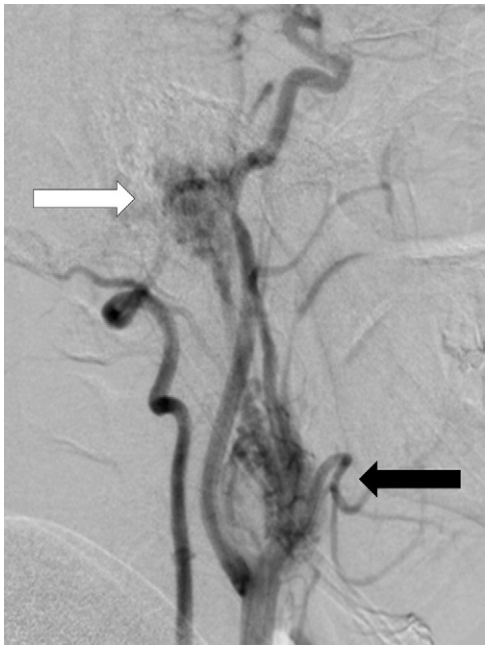

Fig 1. Angiogram of right carotid body (*black arrow*) and glomus jugulare masses (*white arrow*). Further imaging established vascular continuity between the tumors through the ascending pharyngeal artery.

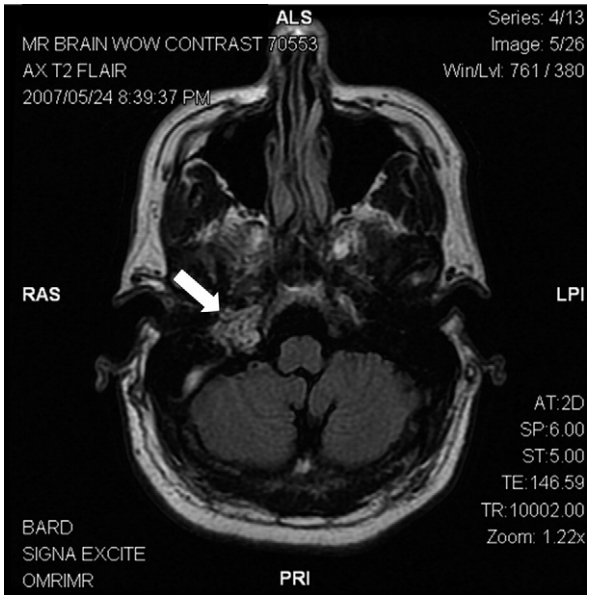

Fig 2. Axial T2-weighted fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) of glomus jugulare tumor (*white arrow*).

center. The patient is presently undergoing surveillance and further testing.

DISCUSSION

Paraganglioma is a term describing neuroendocrine tumors arising outside of the adrenal system and was first used in 1903. These exceedingly rare neoplasms comprise 0.03% of all tumors and 0.6% of head and neck tumors.[4] Within the head and neck, they arise primarily at four sites: the carotid body at the posteromedial wall of the bifurcation (50%-70%), the vagus nerve sheath ganglions (5%), and the chief cells of the jugular bulb and along the auricular nerve within the tympanic space (20%-40%). Head and neck paragangliomas (HNPGLs) are part of the diffuse neuroendocrine system but, unlike their sympathetic abdominal counterpart, the pheochromocytoma, HNPGLs are parasympathetically derived and only rarely secrete catecholamines.[5,6]

The last decade has seen an increased awareness of PGL in conjunction with discovery of gene mutations associated with some of the known familial PGL syndromes. These syndromes typically originate in germline mutations of the A, B, C, and D subunits of the mitochondrial complex II enzyme succinate dehydrogenase (SDH).[7-10] Embedded within the mitochondrial oxidation pathway, interference with SDH is thought to lead to activation of acute and chronic hypoxic pathways, perpetuated stimulation of chemoreceptors, and eventual development of PGLs.[11] In support of this pseudo-hypoxia theory, genetic markers of hypoxia such as HIF-1α and HIF-2β are typically upregulated in familial PGL syndromes. Where the SDHB variant is concerned, however, a pronounced downregulation of these genes is noted.[12,13] This difference in expression may be related to neoplastic potential.

SDHB gene variants are present in approximately 15% of familial PGL patients, demonstrate autosomal dominant biallelic expression without imprinting, and entertain a significantly higher malignancy potential than the typically more benign SDHD and SDHC subtypes (41% vs 2%-4%). The malignancy risk for SDHB carriers varies with neoplasm location, such that a propensity for HNPGLs offers a 12% lifetime risk, while extra-adrenal abdominal PGL (abPGL) manifestation poses a 48% chance of cancer development. SDHB also holds the attributes of being the PGL syndrome with the greatest prevalence of abPGL (50%-67%) and the one least associated with exclusive HNPGL presentation. Multicentric PGL presentation in SDHB carriers is about half that seen with the SDHD subtype (12%-28% vs 30%-74%).[14] When combined, these factors give the patient in this report the distinction of being one of a handful of people recorded with his particularly rare combination of concurrent PGL and a unique representative of HNPGL multicentricity in an SDHB subtype.

Although HNPGLs rarely secrete clinically significant levels of catecholamines, SDHB carriers have an increased incidence of abPGL, and preoperative clinical workup is recommended. Historically, urine metanephrines and plasma catecholamines were utilized in diagnosis, but more recent work indicates that plasma metanephrines are the more sensitive indicator of neuroendocrine tumor presence. Furthermore, noradrenergic phenotyping

Table. Recommendations for an approach to SDHB patient care

Imaging	*Laboratories*	*Outpatient*
Clinical ● **SDHB radionucleotide screening: ^{18}F-FDG-PET is the preferred imaging radiolabel with a sensitivity approaching 100%.[16] Screen for PGL and establish baseline tumor response to resection or radioablation.** ● CTA recommended for cervical tumors. ● MRA recommended for skull base tumors. ○ Angiograms may be useful for assessment of vascular continuity in unilateral masses, embolization, and blood supply to skull base tumors.	● **SDHB noradrenergic screening: the dopamine breakdown product methoxytyramine is particularly elevated in SDHB mutations.[6] Establish baseline tumor secretion activity and noradrenergic phenotyping.** ○ If there are concerns for abPGL or hypertension, baseline plasma metanephrines and catecholamines may be warranted.	● **SDHB surgical clearance: the increased risk of malignancy and the propensity for mixed PGL locales necessitates a thorough preoperative workup with a focus on a staged and progressive treatment approach.** ● Suspect hypertension should be evaluated for primary versus secondary causes, including noradrenergic secretion. ○ Establish suitability for surgery involving baroreceptor organs, major vessels of the skull base and neck, and the potential sacrifice of those vessels.
Perioperative ○ Carotid and internal jugular Doppler and clamp trials may be necessary if there is major vessel compression by the tumor or anticipated operative vessel sacrifice. ○ Angiograms may be warranted if skull base PGL resection is considered due to risk of intracranial hemorrhage.	● For patients of concern, perioperative metanephrines and catecholamines should be monitored due to risk of malignant hypertension with surgical tumor manipulation. ○ Intraoperative labs for HNPGL resection might include parasympathetic metabolites from serotonin and dopamine.	● **SDHB care transition: close communication between radiation, surgical, and oncology specialties must take place to ensure proper transfer of care from surgical intervention to tumor surveillance.** ○ If chemoreceptor structures were manipulated, monitor for baroreceptor failure for 6 months to 1 year postoperatively.[19,20] ○ Postoperative period should include complete neurologic and vascular exams.
Surveillance ● **SDHB radionucleotide surveillance: ^{18}F-FDG-PET is the preferred imaging radiolabel for SDHB patients with a sensitivity approaching 100%. Screening should take place annually with supplementation by MRI and/or CT.** ● MRI and/or CT is recommended in conjunction with whole-body scintigraphy on an annual to biannual basis.	○ Repeat methoxytyramine and metanephrine levels as needed for tumor surveillance and phenotyping. Malignant PGL have been known to express biochemically less mature breakdown products. ○ Further genetic testing may be pursued at this point as needed to include non-familial PGL associated disorders (ie, MEN2A and 2B, NF1, VHL, etc.).	● Primary clinical surveillance should be overseen by an oncology specialist or cancer center with access to specialty radiation and radiologist services, genetic counseling, surgical specialists including vascular and neurosurgical, and surgical oncologists of the head, neck, abdomen, and mediastinal structures.

abPGL, Abdominal paraganglioma; *CT,* computed tomography; *CTA,* computed tomography angiography; *^{18}F-FDG-PET,* ^{18}F-fluoro-2-deoxyglucose-positron emission tomography; *HNPGL,* head and neck paraganglioma; *MRA,* magnetic resonance angiography; *MRI,* magnetic resonance imaging; *PGL,* paraganglioma.

● Highly recommended. Bolded items are SDHB specific.

○ Recommended for use only as needed.

from plasma samples can suggest certain genotypes, as different hereditary PGL syndromes favor particular metabolic profiles. The SDHB mutation, for example, exhibits high levels of the dopamine metabolic byproduct methoxytyramine.[6]

Appropriate monitoring of PGLs is an area of some debate, although a general consensus exists for use of whole-body scintigraphy supplemented by regular imaging with CT and MRI.[15,17,18] Due to the propensity for anticipation within the familial PGL syndromes, carrier screening should start by the first or second decade of life. Traditionally, radiologic screening was done with ^{111}indium pentetreotide single-photon emission computed tomography, but more recent advances utilizing labeled catecholamines such as ^{18}fluorodopamine (^{18}F-FDG) show higher specificity and sensitivity.[15] For SDHB mutations in particular, ^{18}F-FDG-PET is the preferred imaging radiolabel, with a sensitivity approaching 100%.[16] Genetic evaluation is also recommended in cases of positive family history, abPGL, or bilateral presentation of HNPGLs; the increased malignancy potential of the SDHB mutation in particular precludes early screening of offspring. At this time, treatment for metastatic PGL is limited and consists of combined surgical excision, radioablation, chemotherapy, and radiotherapeutics; 5-year survival varies between 35% and 65%.[18] Under a systematic screening and treatment approach,

it can be expected that the disciplines of nuclear medicine, radiology, neurology, radiation-oncology, vascular surgery, neurosurgery, and genetics may be involved in conjunction with regular primary care oversight for the duration of the patient's life.

The patient in this case report came to our practice without a clear long-term plan of care. It was only after the second carotid body resection that the patient was genetically tested, and a plan centered on his unique and aggressive germline mutation was developed. The noradrenergic phenotyping and ^{18}F-FDG-PET surveillance techniques discussed here are recent developments that we include as part of a recommended SDHB care plan (Table). Any PGL treatment plan should be multidisciplinary in design and developed with the goal of accommodating surgical ease of resection, physiologic compensation, generational burden, and the possibility of further tumor development in anatomically noteworthy territory.

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